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One-pot highly stereoselective reduction of β-keto amides to *syn*-γ-aminols

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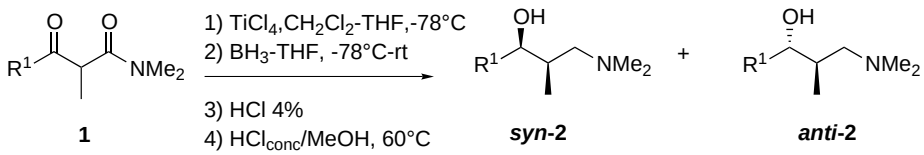
Abstract—In the presence of titanium tetrachloride, the borane/tetrahydrofuran complex can reduce 2-methyl-3-oxoamides into the corresponding *syn*-aminols in good yields and high diastereoselectivity. The use of borane/dimethyl sulfide instead of BH_3/THF allows a partial reduction to *syn*-β-hydroxyamides.

The structural unit of 1,3-aminoalcohol is present with a stereodefined geometry in many compounds having a biological interest.[1] In addition, aminols are useful building blocks in the synthesis of many natural products.[2]

In recent years several procedures for the construction of this functionality, configurationally defined at the 1,3,[3] 2,3[4] and 1,2,3[5] positions, have been proposed. Surprisingly, a simple, general, and efficient solution to the problem of 1,2-stereocontrol is not available. In particular, the only methods reported in the literature for the synthesis of 1,2-*syn*-3-aminols are the regio- and stereoselective ring-opening of epoxy-amines with alanes[6] and the acidic hydrolysis of certain 3,6-dihydro-2*H*-1,3-oxazines.[7] These procedures show good stereoselectivity, but they are rather complex being based on multistep reactions.

We assumed that the diastereoselective double reduction of β-ketoamides could be a very simple approach to obtain *syn*-γ-amino-β-alkylalcohols **2** (Scheme 1). We report here how such a conversion can be accomplished according to a one-pot procedure by using an excess of the BH_3–THF complex in the presence of $TiCl_4$.[8]

It is well established that the reduction of carbonyl bidentate compounds with BH_3–complexes in the presence of $TiCl_4$ proceeds via chelate complex intermediates.[9] It can be reasonably assumed that amide **1** forms a cyclic complex like **3**, by treatment with $TiCl_4$ in dichloromethane–THF at low temperature (see Scheme 2). 1,2-Strain interaction between the methyl and R^1 group favours conformation **3A**. Addition of an excess of the BH_3–THF complex produces the stereoselective reduction of the carbonyl function as the result of an attack of the hydride ion source to the less hindered face of **3A**: very likely this would give a titanium or boron alkoxy amide of type **4**. In order to have a complete reduction of **1** to **4** and in order to promote the further reduction of the amide to the amino function, the mixture was allowed to reach room tempera-



Scheme 1.

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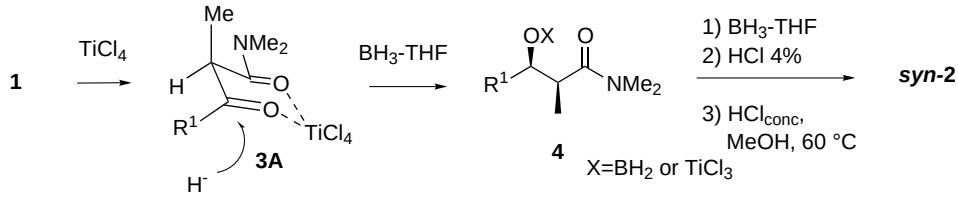


Scheme 2.

ture. Decomposition with diluted HCl gave aminoalcohols as cyclic boron complexes. Further treatment of the crude with methanolic HCl at 60°C for 3 h allows one to obtain *syn*-aminoalcohols **2** in a pure form. We adopted this decomposition procedure since the usual oxidative method (H_2O_2, NaOH, MeOH) fails, due to the presence of a trivalent nitrogen in the substrate.[10]

The reaction has been applied to a significative series of α-methyl-β-ketoamides. As shown in Table 1, yields are generally good and diastereoisomeric ratios vary from high to excellent.[11,12] The reaction works well when R^1 is a phenyl, a *t*-butyl group and a long chain alkyl framework. Slightly lower selectivities were observed in the following cases: (i) when the $A^{1,2}$ strain is low (R^1 = Et, Table 1, entry 1); (ii) when R^1 is a *i*-Pr group (Table 1, entry 2), owing to the occurrence of 1,5-pentane interaction;[13] (iii) when a strong electron withdrawing group such as NO_2 is present in the aromatic ring bound to the carbonyl function (Table 1, entry 7). In the latter case, in fact, the decrease in the electron density at the carbonyl function causes a destabilization of the chelate complex **3**.

Other borane complexes were also tested. The BH_3–py[14] complex works quite well, although the use of this reagent leads to serious problems in the purification of final compounds.

Surprisingly, the BH_3–Me_2S complex[15] allows a very rapid reduction of ketoamides **1** to *syn*-β-hydroxy-α-alkylamides **5** (Scheme 3), however, it fails to accomplish the further reduction of the amide to the amine function. As a consequence this reducing agent can be conveniently employed when the target is the synthesis of *syn*-β-hydroxy-α-alkylamides.[16] A few examples of this reduction are reported in Table 2.

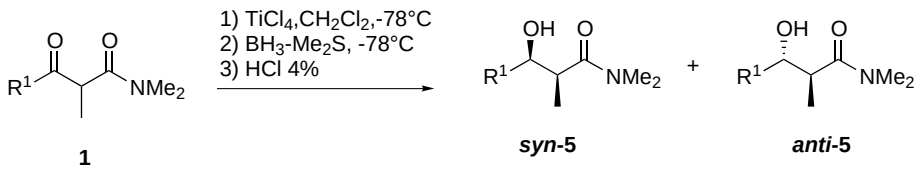
The results reported here show how the reaction proceeds with high diastereoselectivity and in almost quantitative yields.[17,18] It is interesting to note that such a conversion cannot be accomplished with the BH_3–THF method by quenching the reaction at low temperature. The reduction reaction of **1f** for example was stopped after 3 h at −78°C: a mixture containing the unreacted starting material (10%), the monoreduction product (hydroxy amide **5f**, 63%), and the aminol derivative **2f** (11%) was recovered.

Due to the efficiency and the high diastereoselectivity observed, the $TiCl_4$–BH_3–Me_2S method represents a very useful alternative to previously reported procedures.[19]

In conclusion, a simple and highly diastereoselective methodology for the synthesis of aminols with a 1,2-*syn*-stereoconfiguration is proposed. The method makes

Table 1. Diastereoselective one-pot reduction of α-methyl-β-ketoamides **2** to the corresponding *syn*-aminoalcohols **2** with BH_3–THF in THF at −78°C to room temperature

Entry	Starting material	R^1	Product	Yield (%)	*syn*/*anti*
1	**1a**	Et	**2a**	65	96/4
2	**1b**	*i*-Pr	**2b**	60	90/10
3	**1c**	C_5H_{11}	**2c**	89	>99/1
4	**1d**	*t*-Bu	**2d**	83	98/2
5	**1e**	*c*-C_6H_{11}	**2e**	72	95/5
6	**1f**	Ph	**2f**	87	>99/1
7	**1g**	*p*-NO_2-Ph	**2g**	62	90/10
8	**1h**	*p*-Br-Ph	**2h**	69	94/6



Scheme 3.

Table 2. Diastereoselective reduction of α-methyl-β-ketoamides **1** to the corresponding *syn*-α-methyl-β-hydroxyamides **5** with BH_3–Me_2S in CH_2Cl_2 at −78°C

Entry	Starting material	R^1	Product	Yield (%)	*syn*/*anti*
1	**1a**	Et	**5a**	>99	98/2
2	**1b**	*i*-Pr	**5b**	>99	95/5
3	**1c**	C_5H_{11}	**5c**	>99	>99/1
4	**1d**	*t*-Bu	**5d**	>99	98/2
5	**1e**	*c*-C_6H_{11}	**5e**	>99	90/10
6	**1f**	Ph	**5f**	>99	>99/1
7	**1g**	*p*-NO_2-Ph	**5g**	87	91/9
8	**1h**	*p*-Br-Ph	**5h**	>99	>99/1

use of starting materials that are easy available, such as β-ketoamides[20] and very common reducing and chelating agents, such as borane complexes and titanium tetrachloride. Yields are generally very good and diastereoselectivities are either high or excellent. Moreover, the reduction can be limited to the step where β-hydroxyamides are produced by an appropriate choice of the borane reducing agent.

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8. Typical procedure: To a THF (10 ml) solution of β-ketoamide **1** (1 mmol) $TiCl_4$ (1.5 equiv., solution 1 M in CH_2Cl_2) was added at −78°C. After 30 min, BH_3–THF (10 equiv., solution 1 M in THF) was added dropwise. Then the reaction was left to rise to room temperature. After 48 h, the reaction was quenched with aqueous HCl (1 M), left to stir for 1 h and then basified with NaOH (10%) and extracted with CH_2Cl_2. The organic layer was evaporated under reduced pressure. The crude of the reaction was dissolved in MeOH (5 ml/mmol) and HCl conc. (1 ml/mmol) and heated at 60°C. After 3 h, the solvent and the volatile boron derivatives were removed under reduced pressure; then MeOH was added three times to the residues and evaporated. The mixture was basified with NaOH (10%) and extracted with CH_2Cl_2. The organic layer was dried over $MgSO_4$, filtered and evaporated under reduced pressure. The crude products were purified by flash chromatography on aluminium oxide (Et_2O/petroleum ether = 7/3) to give pure aminols **2**.
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12. Spectroscopic data for unknown products follow: **(2*S**,3*S**)-1-(dimethylamino)-2-methyl-3-pentanol (2a)**: ^{1}H NMR ($CDCl_3$, 300 MHz): $\delta=0.80$ (d, 3H, CH_3, $J_{HH}=7.2$), 1.00 (t, 3H, CH_3, $J_{HH}=7.5$), 1.30–1.50 (m, 2H, CH_2), 2.05–2.20 (m, 2H, CH and CH_2), 2.30 (s, 6H, $2CH_3$), 2.65 (dd, 1H, CH, $J_{HH}=12.5$, $J_{HH}=10.7$), 3.1 (bs, 1H, OH), 3.51 (dt, 1H, CH, $J_{HH}=9.0$, $J_{HH}=3.6$); ^{13}C NMR ($CDCl_3$, 75 MHz): $\delta=11.0$ (CH_3), 14.0 (CH_3), 25.0 (CH_2), 34.4 (CH), 45.5 (CH_3), 63.0 (CH_2), 76.5 (CH); **(2*S**,3*S**)-1-(dimethylamino)-2,4-dimethyl-3-pentanol (2b)**: ^{1}H NMR ($CDCl_3$, 300 MHz): $\delta=0.83$ (d, 3H, CH_3, $J_{HH}=6.7$), 0.89 (d, 3H, CH_3, $J_{HH}=6.9$), 1.00 (d, 3H, CH_3, $J_{HH}=6.6$), 1.60–1.75 (m, 1H, CH), 1.80–1.95 (m, 1H, CH), 2.26 (s, 6H, $2CH_3$), 2.29 (dd, 1H, CH, $J_{HH}=12.6$, $J_{HH}=5.4$), 2.49 (dd, 1H, CH, $J_{HH}=12.6$, $J_{HH}=7.2$), 3.0 (bs, 1H, OH), 3.31 (dd, 1H, CH, $J_{HH}=2.4$, $J_{HH}=8.4$); ^{13}C NMR ($CDCl_3$, 75 MHz): $\delta=11.7$ (CH_3), 19.2 (CH_3), 19.6 (CH_3), 30.8 (CH), 33.0 (CH), 46.5 (CH_3), 64.6 (CH_2), 78.9 (CH); **(2*S**,3*S**)-1-(dimethylamino)-2-methyl-3-octanol (2c)**: ^{1}H NMR ($CDCl_3$, 300 MHz): $\delta=0.77$ (d, 3H, CH_3, $J_{HH}=6.9$), 0.88 (t, 3H, CH_3, $J_{HH}=6.8$), 1.20–1.40 (m, 7H, $3CH_2$ and 1H, CH_2), 1.50–1.65 (m, 1H, CH_2), 2.00–2.20 (m, 2H, CH and CH_2), 2.24 (s, 6H, $2CH_3$), 2.56 (dd, 1H, CH, $J_{HH}=13.2$, $J_{HH}=11.7$), 3.50–3.60 (m, 1H, CH), 3.7 (bs, 1H, OH); ^{13}C NMR ($CDCl_3$, 75 MHz): $\delta=14.0$ (CH_3), 14.4 (CH_3), 22.7 (CH_2), 26.3 (CH_2), 32.0 (CH_2), 32.1 (CH_2), 34.5 (CH), 45.8 (CH_3), 63.3 (CH_2), 75.7 (CH); **(2*S**,3*R**)-1-(dimethylamino)-2,4,4-trimethyl-3-pentanol (2d)**: ^{1}H NMR ($CDCl_3$, 300 MHz): $\delta=0.93$ (s, 9H, $3CH_3$), 0.94 (d, 3H, CH_3, $J_{HH}=7.0$), 1.85–2.00 (m, 1H, CH), 2.18 (dd, 1H, CH_2, $J_{HH}=12.4$, $J_{HH}=5.5$), 2.22 (s, 6H, $2CH_3$), 2.34 (dd, 1H, CH_2, $J_{HH}=12.4$, $J_{HH}=7.4$), 2.9 (bs, 1H, OH), 3.42 (d, 1H, CH, $J_{HH}=2.4$); ^{13}C NMR ($CDCl_3$, 75 MHz): $\delta=13.0$ (CH_3), 27.0 (CH_3), 32.2 (CH), 35.4 (C), 46.1 (CH_3), 66.3 (CH_2), 78.9 (CH); **(1*S**,2*S**)-1-cyclohexyl-3-(dimethylamino)-2-methyl-1-propanol (2e)**: ^{1}H NMR ($CDCl_3$, 300 MHz): $\delta=0.88$ (d, 3H, CH_3, $J_{HH}=7.0$), 0.85–1.00 (m, 2H, CH_2), 1.05–1.30 (m, 2H, CH_2), 1.30–1.45 (m, 1H, CH_2), 1.50–1.80 (m, 5H, $2CH_2$ and 1H CH_2), 1.80–1.90 (m, 1H, CH), 2.00–2.10 (m, 1H, CH), 2.23 (s, 6H, $2CH_3$), 2.24 (dd, 1H, CH_2, $J_{HH}=12.6$, $J_{HH}=5.4$), 2.42 (dd, 1H, CH_2, $J_{HH}=12.6$, $J_{HH}=7.2$), 3.36 (dd, 1H, CH, $J_{HH}=2.4$, $J_{HH}=8.7$), 4.0 (bs, 1H, OH); ^{13}C NMR ($CDCl_3$, 75 MHz): $\delta=11.5$ (CH_3), 25.9 (CH_2), 26.1 (CH_2), 26.4 (CH_2), 29.1 (CH_2), 29.8 (CH_2), 32.4 (CH), 40.3 (CH), 46.3 (CH_3), 64.5 (CH_2), 77.2 (CH); **(1*R**,2*S**)-3-(dimethylamino)-2-methyl-1-(4-nitrophenyl)-1-propanol (2g)**: ^{1}H NMR ($CDCl_3$, 300 MHz): $\delta=0.69$ (d, 3H, CH_3, $J_{HH}=6.8$), 2.10–2.20 (m, 1H, CH), 2.37 (s, 6H, $2CH_3$), 2.30–2.60 (m, 2H, CH and CH_2), 4.7 (bs, 1H, OH), 4.97 (d, 1H, CH, $J_{HH}=3.3$), 7.40–7.50 (m, 2H, Ph), 8.15–8.25 (m, 2H, Ph); ^{13}C NMR ($CDCl_3$, 75 MHz): $\delta=14.5$ (CH_3), 35.0 (CH), 45.6 (CH_3), 62.4 (CH_2), 77.7 (CH), 122.8 (CH), 127.6 (CH), 146.9 (C), 150.1 (C); **(1*R**,2*S**)-1-(4-bromophenyl)-3-(dimethylamino)-2-methyl-1-propanol (2h)**: ^{1}H NMR ($CDCl_3$, 300 MHz): $\delta=0.67$ (d, 3H, CH_3, $J_{HH}=6.8$), 2.00–2.10 (m, 1H, CH), 2.33 (s, 6H, $2CH_3$), 2.35–2.50 (m, 2H, CH and CH_2), 4.4 (bs, 1H, OH), 4.78 (d, 1H, CH, $J_{HH}=3.3$), 7.10–7.20 (m, 2H, Ph), 7.40–7.50 (m, 2H, Ph); ^{13}C NMR ($CDCl_3$, 75 MHz): $\delta=15.0$ (CH_3), 34.8 (CH), 45.7 (CH_3), 62.3 (CH_2), 78.0 (CH), 120.5 (C), 128.7 (CH), 130.6 (CH), 141.1 (C).
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16. **Typical procedure**: To a CH_2Cl_2 (10 ml) solution of β-ketoamide **1** (1 mmol) $TiCl_4$ (1.5 equiv., solution 1 M in CH_2Cl_2) was added at −78°C. After 30 min, BH_3–Me_2S (5 equiv., solution 10 M in Me_2S) was added dropwise. After 3 h at −78°C, the reaction was quenched with aqueous HCl (1 M) and extracted with CH_2Cl_2. The organic layer was dried over $MgSO_4$, filtered and evaporated under reduced pressure. The crude products were purified by flash chromatography on aluminiumoxide (Et_2O/petroleum ether = 8/2) to give pure hydroxyamides **5**.
17. Compounds **(2*R**,3*S**)-3-hydroxy-*N*,*N*,2-trimethylpentanamide (5a)**, **(2*R**,3*R**)-3-hydroxy-*N*,*N*,2,4,4-pentamethylpentanamide (5d)**, **(2*R**,3*S**)-3-cyclohexyl-3-hydroxy-*N*,*N*,2-trimethylpropanamide (5e)**, **(2*R**,3*R**)-3-hydroxy-*N*,*N*,2-trimethyl-3-phenylpropanamide (5f)** were recognized by comparison with literature data (see Ref. 19a).
18. Spectroscopic data for unknown products follow: **(2*R**,3*S**) - 3 - hydroxy - *N*,*N*,2,4 - tetramethylpentanamide (5b)**: ^{1}H NMR ($CDCl_3$, 300 MHz): $\delta=0.84$ (d, 3H, CH_3, $J_{HH}=6.8$), 1.03 (d, 3H, CH_3, $J_{HH}=6.6$), 1.11 (d, 3H, CH_3, $J_{HH}=7.1$), 1.65–1.80 (m, 1H, CH), 2.85 (dq, 1H, CH, $J_{HH}=7.1$, $J_{HH}=2.1$), 2.95 (s, 3H, CH_3), 3.05 (s, 3H, CH_3), 3.40 (dd, 1H, CH, $J_{HH}=9.0$, $J_{HH}=2.1$), 4.7 (bs, 1H, OH); ^{13}C NMR ($CDCl_3$, 75 MHz): $\delta=9.3$ (CH_3), 18.6 (CH_3), 19.2 (CH_3), 30.0 (CH), 35.2 (CH_3), 35.6 (CH), 37.1 (CH_3), 76.6 (CH), 177.6 (C); **(2*R**,3*S**)-3-hydroxy-*N*,*N*,2-trimethyloctanamide (5c)**: ^{1}H NMR ($CDCl_3$, 300 MHz): $\delta=0.88$ (t, 3H, CH_3, $J_{HH}=6.8$), 1.13 (d, 3H, CH_3, $J_{HH}=7.1$), 1.20–1.35 (m, 6H, $3CH_2$), 1.40–1.60 (m, 2H, CH_2), 2.62 (dq, 1H, CH, $J_{HH}=7.1$, $J_{HH}=2.1$), 2.94 (s, 3H, CH_3), 3.04 (s, 3H, CH_3), 3.80–3.90 (m, 1H, CH), 4.6 (bs, 1H, OH); ^{13}C NMR ($CDCl_3$, 75 MHz): $\delta=9.4$ (CH_3), 13.8 (CH_3), 22.4 (CH_2), 25.5 (CH_2), 31.9 (CH_2), 33.6 (CH_2), 35.1 (CH_3), 37.2 (CH_3), 38.5 (CH), 71.0 (CH), 177.8 (C); **(2*R**,3*R**)-3-hydroxy-*N*,*N*,2-trimethyl-3-(4-nitrophenyl)-propanamide (5g)**: ^{1}H NMR ($CDCl_3$, 300 MHz): $\delta=0.98$ (d, 3H, CH_3, $J_{HH}=7.2$), 2.86 (dq, 1H, CH, $J_{HH}=7.2$, $J_{HH}=2.2$), 3.00 (s, 3H, CH_3), 3.06 (s, 3H, CH_3), 5.18 (d, 1H, CH, $J_{HH}=2.2$), 5.5 (bs, 1H, OH), 7.50–7.60 (m, 2H, Ph), 8.15–8.25 (m, 2H, Ph); ^{13}C NMR ($CDCl_3$, 75 MHz): $\delta=9.2$ (CH_3), 35.5 (CH_3), 37.4 (CH_3), 40.9 (CH), 72.5 (CH), 123.4 (CH), 126.9

(CH), 147.0 (C), 149.2 (C), 176.7 (C); **(2*R***,3*R***)-3-(4-bromophenyl) - 3 - hydroxy - *N*,*N*,2 - trimethylpropanamide (5h)**: ^{1}H NMR ($CDCl_3$, 300 MHz): $\delta = 0.99$ (d, 3H, CH_3, $J_{HH} = 7.2$), 2.79 (dq, 1H, CH, $J_{HH} = 7.2$, $J_{HH} = 2.4$), 2.97 (s, 3H, CH_3), 3.02 (s, 3H, CH_3), 3.5 (bs, 1H, OH), 5.04 (d, 1H, CH, $J_{HH} = 2.4$), 7.20–7.30 (m, 2H, Ph), 7.40–7.50 (m, 2H, Ph); ^{13}C NMR ($CDCl_3$, 75 MHz): $\delta = 9.6$ (CH_3), 35.1 (CH_3), 37.0 (CH_3), 41.1 (CH), 72.5 (CH), 120.5 (C), 127.5 (CH), 130.8 (CH), 140.7 (C), 176.5 (C).

19. (a) Taniguchi, M.; Fujii, H.; Oshima, K.; Utimoto, K. *Tetrahedron* **1993**, *49*, 11169–11182; (b) Fujita, M.; Hiyama, T. *J. Am. Chem. Soc.* **1985**, *107*, 8294–8296; (c) Fujita, M.; Hiyama, T. *J. Org. Chem.* **1988**, *53*, 5405–5414; (d) Fujita, M.; Hiyama, T. *J. Org. Chem.* **1988**, *53*, 5415–5421; (e) Fujita, M.; Hiyama, T. *Org. Synth.* **1990**, *69*, 44–53; (f) Fujii, H.; Oshima, K.; Utimoto, K. *Tetrahedron Lett.* **1991**, *32*, 6147–6150.
20. β-Ketoamides with no enolizable R^1 group (**1d**, **1f**, **1g**, **1h**) were synthesized in high yields from the α-anion of *N*,*N*-dimethyl propionamide and the appropriate ester following the same procedure adopted for the synthesis of β-ketophosphineoxides (see: Bartoli, G.; Bosco, M.; Sambri, L.; Marcantoni, E. *Tetrahedron Lett.* **1996**, *37*, 7421); β-ketoamides with enolizable R^1 group (**1a**, **1b**, **1c**, **1e**) were synthesized according to Ref. 19a.